Title

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Journal

Clinical pharmacology and therapeutics, 96(1)

ISSN

0009-9236

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Publication Date

2014-07-01

DOI

10.1038/clpt.2014.63

Peer reviewed

HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

Clin Pharmacol Ther. 2014 July ; 96(1): 27–35. doi:10.1038/clpt.2014.63.

Sorafenib Dose Escalation is Not Uniformly Associated with Blood Pressure Elevations in Normotensive Patients with Advanced Malignancies

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Abstract

Hypertension with vascular endothelial growth factor (VEGF) receptor inhibitors is associated with superior treatment outcomes for advanced cancer patients. To determine whether increased doses of sorafenib cause incremental increases in blood pressure (BP) we measured 12-hour ambulatory BP in 41 normotensive advanced solid tumor patients in a randomized dose escalation study. After 7 days' sorafenib (400mg BID) mean diastolic BP (DBP) increased in both study

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Note: This work was presented in part as an abstract at the American Society of Clinical Oncology Annual Meeting, June 5, 2011, Chicago, Illinois, USA.

Author Contributions

S.K., Y.W., T.G.K., M.J.R., and M.L.M. wrote the manuscript
T.G.K., J.J.W., G.L.B., M.J.R., and M.L.M. designed the research
S.K., M.R.L., L.K.H., V.T., M.A.R., E.E.W.C., G.F.F., M.J.R., and M.L.M. performed the research
S.K., T.G.K., K.W., V.T., M.A.R., and M.L.M. analyzed the data

Conflicts of Interest/Disclosure

The biomarker testing in this study was funded in part by Bayer, Inc. MLM is a paid consultant to Amgen and has received research funding from Roche/Genentech, AbbVie, Amgen, and Astellas. MJR is a paid consultant to Roche/Genentech. GLB is a consultant for AbbVie, Takeda, Bayer, Daichi-Sankyo, Medtronic, Relypsa.

groups. After dose escalation, group A (400mg TID) had marginally significant further increase in 12-hour mean DBP (p=0.053) but group B (600mg BID) did not achieve statistically significant increases (p=0.25). Within groups, individuals varied in BP response to sorafenib dose escalation, but these differences did not correlate with changes in steady state plasma sorafenib concentrations. These findings in normotensive patients suggest BP is a complex pharmacodynamic biomarker of VEGF inhibition. Patients have intrinsic differences in sensitivity to the BP elevating effects of sorafenib.

Keywords

sorafenib; blood pressure; VEGFR; angiogenesis inhibitors; biomarker; neoplasms

INTRODUCTION

Hypertension is a common, mechanism-based effect of VEGF-signaling-pathway (VSP) inhibitors. Prior investigations suggested that blood pressure (BP) might be a valid, quantitative biomarker of VSP inhibitor pharmacodynamic effects (1–7). Several more recent studies have found that patients who develop hypertension with VSP inhibitor treatment have better progression-free and overall survival than those who do not (8–10). These findings have led investigators to speculate that escalating the dose of VSP inhibitors in order to increase the number of patients who develop hypertension with treatment might lead to better outcomes.

The simplicity of the “dose-to-hypertension” strategy is appealing. But among dose, hypertension, and improved outcomes for VEGF signaling inhibition therapy there are incompletely understood, complex, elements to the relationship (8, 11, 12). To inform effective implementation of this strategy with VEGF signaling pathway inhibitors broadly, it will be helpful to resolve these relationships. We had the opportunity to conduct this prospective investigation with sorafenib and addressed 4 considerations in the dose/blood pressure response/efficacy relationship relevant to this compound.

1) Pharmacokinetic variance

there is significant interindividual variance in sorafenib plasma pharmacokinetics(13, 14). Some patients will achieve increased drug exposure with increased dose while others will have already achieved maximum achievable plasma concentrations with standard doses of sorafenib. In others drug exposure will of necessity be limited due to intolerable side effects. We hypothesized that a subset of patients with initially sub-maximal sorafenib exposure might achieve higher drug levels and associated higher magnitude changes in blood pressure by increasing their dose. We did not know how this escalation in dose would affect tolerability. We expected in patients who already achieved maximum plasma concentrations with standard doses that dose escalation would not have any additional pharmacodynamic effects or associated adverse effects. More intensive study would enable us to estimate the frequency of patients who could achieve higher exposures with higher doses.

2) Pharmacodynamic variance and dose escalation response

prior studies of sorafenib(4), sunitinib(15), and levantinib(2) demonstrated significant interindividual variance in the magnitude of the change in BP with VEGFR2 kinase inhibitor therapy and little association between plasma drug concentrations and the magnitude of BP response. Most patients have some BP response, but the dose/BP response within individuals has not been studied. It is not known how frequently dose escalation within the individual patient will achieve additional elevations in BP.

3) Effects of pre-existing hypertension on the PK/PD relationship

Hypertension is common among cancer patients and typically not a life-threatening condition. In most trials of VSP inhibitors pre-existing hypertension has not been an exclusion criterion. For patients with pre-existing hypertension that was attentively controlled with medical management prior to initiating sorafenib, there was no statistically significant difference in mean change in BP with sorafenib therapy compared to normotensive patients(4). A subsequent study of sunitinib had similar findings(16). In trials where the antihypertensive therapy management was not as carefully controlled, the variable control of BP in patients with pre-existing hypertension and the effects of their pre-treatment antihypertensive therapy on VEGF-inhibitor-induced elevations in BP are unclear.

4) BP measurement imprecision obfuscating the PK/PD relationship

finally, the use of infrequent office-based BP measurements in some published studies introduces significant imprecision in measurement and confuses data interpretation. In studies of groups of patients, mean BP values for each group can be used to infer some pharmacologic effects. But to understand inter-individual differences in these PK/PD relationships requires accurate determination of which BP changes are due to drug exposure(17), which to normal fluctuation of BP or routinely imprecise office BP measurement(18, 19).

We therefore conducted this prospective, randomized dose-escalation pharmacodynamic assessment trial in advanced solid tumor patients to address these elements of interpatient variance in the dose-to-blood pressure relationship for sorafenib. The overall purpose of the trial was to determine whether standard dosing of sorafenib (400 mg twice daily) in advanced solid tumor patients followed by either of two dose escalation schemes (400 mg three times daily or 600 mg two times daily) would lead to measurable additional increases in mean 12-hour ambulatory BP (ABP), and to assess the safety and tolerability of these higher dose treatment regimens. To eliminate pre-existing hypertension and anti-hypertensive therapy as variables in the analysis we enrolled exclusively patients who were normotensive and not receiving any antihypertensive therapy. To ensure that dose escalation was reserved exclusively for patients most likely to tolerate it, we conducted a one-week run-in period to exclude any subjects who developed immediate evidence of hypertension or other ≥ grade 2 adverse effects (AEs). Patients were then randomized to one of two different dose escalation regimens. We employed a one-week washout period so that within individual changes in BP could be compared based on dose and exposure.

To address tolerability of dose escalation: subjects were re-evaluated after one week at the higher dose and every two weeks thereafter for the first 6 weeks of treatment. To minimize measurement imprecision, we employed ABP measurements and assessed the quantitative effects of sorafenib on 12-hour mean BP.

RESULTS

Patient characteristics

Of the 94 eligible patients with advanced metastatic disease for whom no superior alternative treatment options were available, 62 were determined to be evaluable with all 4 ABP measurements collected. From those 62 patients, 41 were randomized to dose escalation (Arm A (400 mg TID), n=20 and Arm B (600 mg BID), n=21 (Table 1).

Safety and efficacy of sorafenib

Higher doses of sorafenib were well tolerated in only a small subset of patients. Seventeen patients experienced AEs in the first week of treatment with 400 mg twice daily and to ensure patient safety, per protocol, this prohibited randomization to a dose escalation arm of the study. Eight patients had ≥ grade 2 lipase, 4 had ≥ grade 2 hypophosphatemia, 2 had ≥ grade 2 hypertension, 1 had grade 2 hand-foot syndrome, 1 had grade 3 hemoptysis and 1 had grade 3 prothrombin time. Beginning with Day 22, the 41 subjects in escalated dose Arms A and B began to develop ≥ grade 2 AEs other than hypertension that warranted dose reductions (Table 2). Ten (5 in the each arm) patients required dose reductions in the first 3 weeks after receiving escalated dose sorafenib. An additional 12 (7 in the Arm A and 5 in the Arm B) patients required dose reduction in the next 3 weeks. Of the 19 patients who continued at the escalated dose after 8 weeks on study, 17 developed progressive disease and discontinued the trial by 12 weeks. Only 2 patients remained on the escalated, randomized dose of sorafenib for 6 months without any interruptions.

Effects of sorafenib dose on blood pressure

Consistent with prior reports on ABP measurements in sorafenib-treated patients(4), this independent cohort of normotensive patients had significant elevations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) within the first week of sorafenib treatment at standard dose (Table 3). The time course of DBP changes was consistent with expectations (Figure 1). There was a clear but incomplete return toward baseline DBP in both Arms by Day 14, 15. Paired t-tests for the change in DBP between the end of the first week (Day 7, 8) at 400 mg twice daily and the DBP at the end of the week of escalated dose (Day 21, 22) demonstrated marginally statistically significant increase for Arm A 3.0 mmHg ($p = 0.053$, 95% CI −0.04, 6.14) and no statistically significant increase for Arm B, 1.5 mmHg ($p = 0.25$, 95% CI −1.11, 4.06).

Heterogeneity of the blood pressure response to sorafenib

In this normotensive cohort of advanced solid tumor patients, the distribution of magnitude of changes in BP after 1 week of standard dose therapy was similar to that observed in prior studies(4) (Figure 2). The mean increase in DBP by Day 7, 8 was 8.0 mmHg (standard deviation of 6.2 mmHg). Of all 41 randomized evaluable patients, 11 appeared resistant to

the sorafenib-induced DBP elevation. Meanwhile 5 patients had DBP elevations of at least 15 mmHg, with 2 having increases of 20 mmHg or more. Also similar to a prior study (4), there was no evidence of correlation between plasma sorafenib concentrations (C_{avess}) and the magnitude of change in DBP (r = 0.00; p = 0.66) (Supplementary Figure 1). Similarly, there was no evidence of correlation between the baseline DBP and the magnitude of change in DBP (r =0.00; p = 0.71) (Supplementary Figure 2). There was no significant association of the magnitude of change in DBP with age, sex, self-reported race ("White" vs. Others), or body mass index (BMI).

Blood pressure response patterns and sorafenib plasma exposure

The assigned doses did not increase BP uniformly and we observed 3 different patterns of BP response (Figure 3). We categorized these responses as: BP-resistant, dose-sensitive, and dose-insensitive. BP-resistant was defined as those subjects who had no measurably significant increase in mean BP after dosing at 400 mg twice daily after the first week and still no measurable increase after receiving the escalated dose sorafenib during the third week (3 patients) (Figure 3a). Dose-sensitive comprised two groups of patients: 1) those who had no detectable increase in BP after the first week of standard dose therapy but who then had a detectable increase in BP with the escalated dose, or 2) those who had a detectable increase in BP after the first week of standard dose therapy and a proportional additional increase in BP after receiving the escalated dose during the third week (11 patients) (Figure 3b). The remaining patients had detectable increases in BP after one week of standard dosing, but no further increase with escalated doses (27 patients) (Figure 3c).

There was no relationship between BP response and plasma sorafenib concentrations after one week at standard dosing. This finding did not exclude the possibility that BP would measurably increase in the subjects who could achieve higher plasma exposures with dose escalation. To test this hypothesis, we performed a regression analysis for the Day 21, 22 DBP with main effect terms for the Day 7, 8 DBP and the change in sorafenib C_{avess} between Days 7, 8 and 21, 22. Among all evaluable randomized patients, there were 37 with complete plasma sampling (8 plasma samples in total: 2 samples each on Days 7 and 8 and 2 samples each on Days 21 and 22) and uninterrupted administration of sorafenib. In this analysis, the change in C_{avess} between Days 21, 22 and 7, 8 was not a significant covariate (p = 0.78) (Figure 4). Similarly, it was not a significant covariate for SBP (p = 0.67).

These findings of no association between plasma sorafenib exposure and change in BP were consistent with findings from prior studies with VEGFR2 kinase inhibitors (2, 4, 15). A recent investigation (16) of predictive biomarkers of hypertension in sunitinib-treated patients identified an association between grade 3 hypertension and the C allele of a common single nucleotide polymorphism (rs2070744/-786 T->C) in the gene that encodes endothelial nitric oxide synthase, *NOS3*. This SNP has biological plausibility as a determinant of blood pressure response to inhibition of the VEGF signaling pathway. VEGF signaling post-translationally modifies endothelial nitric oxide synthase (eNOS) to increase production of nitric oxide(20, 21). When eNOS inhibitors are administered to animals, similar changes in BP are detected as when VEGFR inhibitors are administered(22). The C allele of rs2070744 has been previously demonstrated to lead to reduced expression of

eNOS(23), reduce cardiac nitrite/nitrate production during administration of acetyl choline(24), and has been associated with coronary vasospasm in post-myocardial infarction patients(23, 25). In a combined 125 patient sample of the patients in this and a prior study of sorafenib and ambulatory blood pressure changes we typed rs2070744. The genotype distribution was: 53 (42%) TT, 54 (43%) CT, and 18 (15%) CC. In both additive and dominant models we found no evidence of association of the C allele with either DBP (p=0.49) or SBP (p=0.52) changes when steady state sorafenib concentrations were reached with 400mg sorafenib twice daily.

Therapeutic effects of sorafenib in a heterogeneous advanced solid tumor patient population

Of the 41 evaluable randomized patients, 27 continued to receive escalated sorafenib beyond 12 weeks. Of these 27 patients,11 (6 in Arm A, 5 in Arm B) stayed ≥ 6 months on sorafenib. Eight patients (2 in Arm A, 3 from Arm B,) stayed on sorafenib for more than 12 months, but only 2 at a dose greater than 400 mg twice daily. The distribution of time on study, ranged from 1–37 months for all evaluable randomized patients (mean = 6.4 and SD = 7.2 months). The best response (at any point) was one breast cancer patient who had a partial response and stayed on sorafenib for 8.5 months. She had a 10 mmHg increase in her ambulatory DBP during week one and met grade 2 hypertension criteria and was not randomized to higher dose sorafenib

For the 27 patients with diseases that have had some evidence of single agent activity with VEGF-signaling pathway inhibitors: breast, head & neck, neuroendocrine, non-small cell lung, renal, sarcoma, thyroid, or uterine malignancies, there was no statistically significant correlation between maximum C_{avess} and time on study or between maximum change from baseline DBP during the first month of treatment and time on study.

DISCUSSION

This dose-ranging study of sorafenib with ABP measurements in advanced cancer patients revealed the complexity of interindividual differences in BP response to VEGF-signaling inhibition. The first week standard dose, second week wash-out, third week re-treat study design confirmed that BP is a pharmacodynamic biomarker for VEGF-signaling inhibition. But, among this cohort of normotensive patients, the differences among individual BP responses to the first week of standard dose sorafenib therapy was similar to that observed previously(4). Approximately 20% have no BP elevation and 15% have DBP increases greater than 15 mmHg. As described in the prior study there was no association between this BP response variance and baseline BP or the variance in sorafenib plasma concentrations. That study enrolled 19 subjects with renal carcinoma, all of whom had prior nephrectomy, and yet there was no difference in the mean blood pressure changes among those patients compared to all the other patients in that trial.

Similar heterogeneity of BP responses to VEGF-signaling inhibition and independence of this response from plasma drug concentrations has been observed in studies of axitinib(26) and sunitinib(3). These findings imply that individual patients have intrinsic sensitivity/ resistance to the BP elevating effects of VEGF-signaling inhibition, but the specific factors

that determine this response remain unidentified. Some studies have suggested a role for germline genetic polymorphisms(16, 27, 28). Acknowledging the weaknesses of a candidate gene variant approach, we tested for the effect of one previously reported SNP associated with hypertension in sunitinib patients. With the quantitative phenotype of blood pressure change this polymorphism had no effect. However the consistent phenotyping in this trial and the prior study should support future work to assess more comprehensively the effects of candidate gene variants and other relevant factors in multivariate models of intrinsic sensitivity and resistance of patients to sorafenib-induced BP elevation.

The randomly assigned escalated doses of sorafenib did not routinely achieve further elevation of BP. Our examination of individual patient ambulatory BP profiles and sorafenib plasma concentrations suggests an added layer of interpatient differences in the BP response. Some are completely resistant to the BP-elevating effects of VEGF-inhibition, some have maximum BP response to standard dose sorafenib, and some have proportional increases in BP when the dose is increased. Given differences in initial BP response to standard dosing and the additional interpatient differences in responses to dose escalation, further use of BP response as a method to titrate a patient's dose will be challenging.

For sorafenib, characterizing this relationship further is complicated. A shortcoming of our study was the incomplete pharmacokinetic sampling strategy. We expected full sampling concomitant with ambulatory BP monitoring in this patient population to be too onerous on the advanced solid tumor patient volunteers to complete accrual to the trial. We applied to our sparsely sampled data a recently published population pharmacokinetic model(14) but AUC estimates with this model did not decrease the pharmacokinetic variance among our patients compared to using the C_{avess} data directly. A more complete pharmacokinetic sampling strategy or accrual of more patients might have detected a subtle effect of sorafenib exposure on BP response. However, among the patients with dose-sensitive BP response patterns, only 4 were able to continue sorafenib at the escalated dose up to 8 weeks. These findings are consistent with the variance in BP elevating effects of sorafenib being primarily biological system-based rather than drug-specific.

The richness of the data collected in this sorafenib trial could guide the discovery of predictive markers for VEGF-signaling inhibitors. A more integrated analysis of germline genetic factors, cardiovascular physiology, and molecular effects of VEGF signaling inhibition should lead to better understanding of the mechanistic basis for interindividual differences in response to these drugs. In turn, the biomarkers developed from this strategy should lead to a better therapeutic index for anticancer drugs that disrupt VEGF signaling.

METHODS

Patients

A total of 94 patients with advanced solid tumors were recruited at the University of Chicago Hospitals from May 2007 to August 2011. The study was closed when at least 20 subjects each in Arms A and B met evaluability criteria for the study endpoints. All subjects provided written informed consent, and met all of the inclusion criteria and none of the exclusion criteria. Inclusion criteria were: life expectancy ≥ 12 weeks, age ≥ 14 years or

weight of at least 45 kg in pediatric patients; Eastern Cooperative Oncology Group Performance Status rating of 0 or 1; acceptable organ and marrow function by prespecified laboratory measures. Patients were excluded if pretreatment BP was >140/90 mmHg or required an antihypertensive agent to maintain normal BP, had cardiovascular or cerebrovascular disease or had prior sorafenib therapy. Patients with unstable conditions, recent open surgical procedures, seizure disorders, or immune deficiency also were excluded. Screening BP and all standardized office BP measurements were performed according to American Heart Association guidelines(29) with an International Protocol-certified device (Omron HEM-747-IC). The study protocol (NCT00436579) was approved by the Institutional Review Board of the Biological Sciences Division of the University of Chicago.

Treatment

The study schema is presented in (Figure 5). All subjects initially received sorafenib 400 mg orally twice daily for 7 Days and did not take drug for the next 7 Days. The one-week washout was employed to isolate the BP elevation effects of escalated dose sorafenib from the previously administered standard dose sorafenib vs. and to demonstrate the sorafenib administration-dependent effects on BP. Those who tolerated the first week of treatment and did not have at least one ≥ Grade 3 toxicity and no ≥ Grade 2 hand-foot skin reaction, rash, or hypertension, were randomized, 1:1, to receive 400 mg orally three times daily (Arm A), or 600 mg twice daily (Arm B). When tolerability was established after Day 8, the study nurse would open the dose Arm assignment envelope for the patient. Randomized treatment assignment sequences were produced by the study statistician using the random number generator in Stata and printed in the closed envelopes provided to the study nurse. All subjects restarted sorafenib at the assigned treatment dose with the evening dose on Day 15.

Arm C (no dose escalation) comprised 2 groups of patients. The protocol initially randomized patients who tolerated therapy to Arms A, B, or C, 2:2;1, and during this phase, 4 subjects without toxicities during the first week of treatment were randomized to Arm C and received 400 mg twice daily. As more patients than we initially projected experienced grade ≥2 toxicities during the initial week of treatment, we amended the protocol and stopped randomizing patients to Arm C. However, many patients enrolled in the trial in order to receive access to sorafenib for their treatment of advanced cancer. Ultimately, 17 patients could not be safely randomized to dose escalation, and were re-treated with the standard 400 mg twice daily dose. These 21 (4+17) patients excluded from the analyses presented here. Subjects who completed each of the four scheduled ABP monitoring sessions without missing/changing treatment during the prior week were considered evaluable for the study endpoints. After treatment assignment, sorafenib was administered continuously as tolerated.

Safety and tolerability

During the first 8 weeks of the study, subjects underwent physician evaluations and laboratory data review biweekly. Every 21 days of therapy was considered a treatment cycle. After the initial computed tomography (CT) imaging evaluation at week 8, physician evaluations continued every 3–4 weeks thereafter. All toxicities were graded using the NCI

Common Terminology Criteria for Adverse Events Version 3.0(30), except for hypertension and rash where departures from CTCAE guidelines were designed to clarify ambiguities of required treatment response assessments. The study protocol had guidelines for dose modifications, minimally acceptable dosing delays, managing and reporting toxicities.

Ambulatory Blood Pressure Measurement

To determine precisely the magnitude of BP changes on different doses of sorafenib, subjects underwent serial 12-hour ABP monitoring. The Oscar 2 device (Sun Tech Medical, Morrisville, NC, USA) was applied with an appropriately sized cuff and programmed to collect measurements approximately every 10 minutes. All ABP sessions began between 7 AM and 11:30 AM, and had a minimum of 50 measurements to meet criteria as an evaluable session. ABP monitoring was conducted at baseline (BL) (1–10 days before beginning of treatment), after 7 Days of 400 mg twice daily therapy, after 7 Days wash-out, and after 7 Days treatment on the assigned dose escalation (or 400 mg twice daily). For each subject the unweighted mean of all measurements over the 12 hour interval was used as a summary for all analyses. Intradevice and inter-device measurement variability was assessed throughout the study with a reference volunteer subject. Systolic measurements were typically within 3 mmHg, and diastolic measurements were within 2.5 mmHg.

Plasma Concentration Measurements and Pharmacokinetics

Blood samples were collected into sodium-heparinized tubes twice daily on Days 7, 8, 21, and 22. Multiple prior studies have demonstrated significant intra- and inter-individual variance in sorafenib pharmacokinetics(13, 14, 31–36). These studies have demonstrated that traditionally specified times for peak and trough sample collections are erratic. We therefore specified simply that at least 2 samples be collected on each of two days at steady state, separated by no less than 4 hours. On study Day 22, we attempted to reach “trough” concentrations by having subjects not take the morning dose until all blood collection was completed, but this strategy did not significantly lower Day 22 concentrations of this long-half-life compound compared to Day 21 measurements. Plasma was separated by centrifugation at 1300g for 15 minutes at 4°C and stored at −80°C. Total sorafenib concentrations were determined by a validated spectroscopic method(33). Unbound sorafenib concentrations were determined by a validated assay(32).

These sparsely collected data were initially fit to a published population pharmacokinetic model for sorafenib(14). As the model parameter estimates were no more precise than using average concentrations of total plasma sorafenib at steady state (C_{avess}), this measurement was used in all subsequent analyses. The unbound fraction was low and highly correlated with total sorafenib concentrations, which was similar to the initial findings(32). Therefore all pharmacokinetic/pharmacodynamic interactions were analyzed using total sorafenib plasma concentrations.

Genotyping

Germline DNA samples were collected from patients enrolled in this and a previously published study(4). Subjects from both studies with ABP measurements at baseline and after one week of sorafenib at 400 mg twice daily (n=127) were included in the analysis. They

were genotyped for *eNOS*-786T>C SNP (rs2070744) with the Taqman® allelic discrimination assay (assay ID: C_15903863_10, Applied Biosystems, Carlsbad, CA). Of the 127 subjects, 125 had informative genotyping results (98% success rate) and these 125 were included in the genotype/phenotype association analysis.

Statistical Analysis

For evaluable subjects mean BP values were calculated from all measurements in the approximately 12 hour day-time session, providing a summary measure for each patient. As previously noted(4), independent analysis of ambulatory systolic blood pressure (SBP) effects revealed no significant differences from the analyses conducted on diastolic blood pressure (DBP). DBP values had lower variance and proportionally greater magnitude changes, so all pharmacodynamic evaluations related to sorafenib are reported with DBP. As a conservative estimate of the limits of quantitation of change in DBP by our devices, changes in DBP less than 5.0 mmHg (twice the typical intraindividual variance of 2.5 mmHg) were considered to be “no change.”

The significance of DBP changes from Day 7, 8 (end of standard dose) to Day 21, 22 (end of escalated dose) in each arm was determined by paired t-test. Pearson’s correlation coefficient was used for associations among different continuous measurements (eg. change in DBP and age). Multiple regression analysis was performed to explore the relationship between Day 21, 22 BP levels and plasma sorafenib concentrations Statistical significance was defined as $p < 0.05$.

Sorafenib C_{avess} for each patient was generated from the mean of all 4 concentration measurements on Days 7 and 8 for the first treatment interval and Days 21 and 22 for the second interval for each subject. To estimate total plasma sorafenib AUC from the published population pharmacokinetic model, code was provided by William D. Figg(14) and analyses performed with NONMEM version VI level 2.0 (ICON Development Solutions, Hanover, MD) compiled by Intel Visual Fortran compiler version 10 (Intel Corporation, Santa Clara, CA). All statistical analyses were performed with Stata 12 (StataCorp LP, College Station, Texas, USA). Association tests by quantitative trait analysis were performed with PLINK (v1.07) (http://pngu.mgh.hardvard.edu/purcell/plink/)(37) to assess the relationship between rs2070744 and changes in ambulatory BP. Figures were generated with GraphPad (Software, Inc., La Jolla, California) or Spotfire (TIBCO® Spotfire, Somerville, Massachusetts, USA).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: This project was supported by U.S. National Institutes of Health grants: K23CA124802 NCI Career Development Award (MLM), U01CA69852 supported by the Cancer Therapy Evaluation Program of the NCI (MJR), NIGMS U01GM61393 Pharmacogenetics of Anticancer Agents Research Group (MJR and MLM), a protocol-specific project award from the University of Chicago Comprehensive Cancer Center, and the University of Chicago Comprehensive Cancer Center Clinical Pharmacology Core Laboratory. Additional support was provided by a CALGB Foundation Faculty Fellowship (MLM), the Conquer Cancer Foundation of the American

Society of Clinical Oncology (MLM and MJR), research funding from Bayer, Inc., and by the Analytical Pharmacology Core of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NIH grants P30 CA006973 and UL1 RR025005, and the Shared Instrument Grant (1S10RR026824-01)). YW was supported by an internal grant from the University of Chicago Biological Science Division.

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Study Highlights

What is the current knowledge on the topic?

Hypertension is a common adverse effect of VEGF signaling pathway (VSP) inhibitors, and has been associated with improved treatment outcomes in several studies.

What question this study addressed?

This study used ambulatory blood pressure monitoring to determine precisely the dose/response relationship of sorafenib with blood pressure, in advanced cancer patients who had normal blood pressure prior to treatment and could tolerate standard dosing.

What this study adds to our knowledge?

We identified different patterns of pharmacodynamic sensitivity or resistance to the blood-pressure elevating effects of VSP inhibition.

How this might change clinical pharmacology and therapeutics?

This study reveals the complexity of factors affecting the therapeutic index of new anticancer agents intended to disrupt selectively the tumor vasculature.

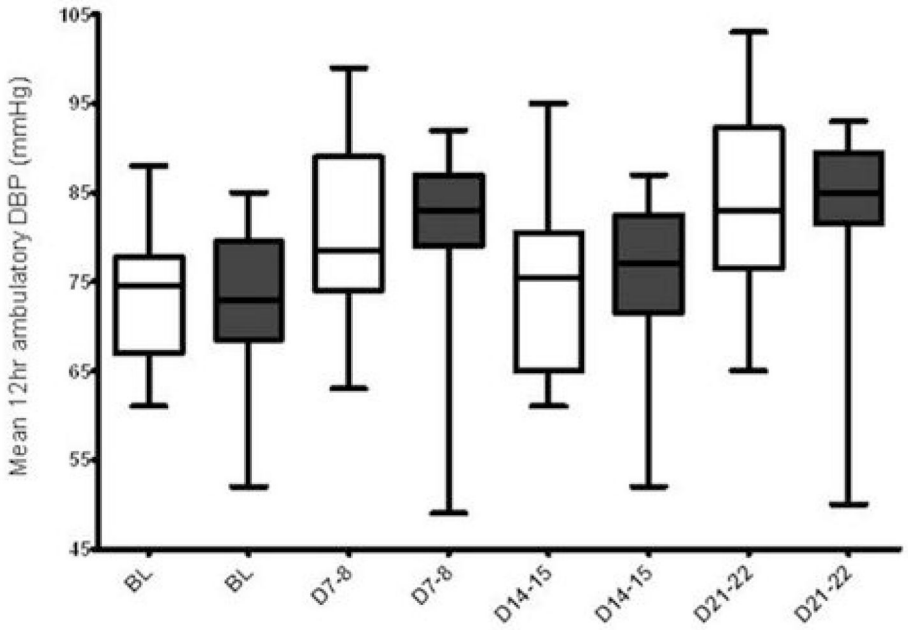

Figure 1. Ambulatory Blood Pressure by Study Arm

Boxplots depict minimum, first quartile, median, third quartile and maximum of DBP for each study arm at baseline (BL), Day 7–8 (D7–8), after the 7 Day washout (D14–15), and after 7 Days at the assigned dose (D21–22). (White boxes = Arm A 400 TID, Dark gray boxes = Arm B 600 BID); DBP = diastolic blood pressure, mmHg = millimeters mercury

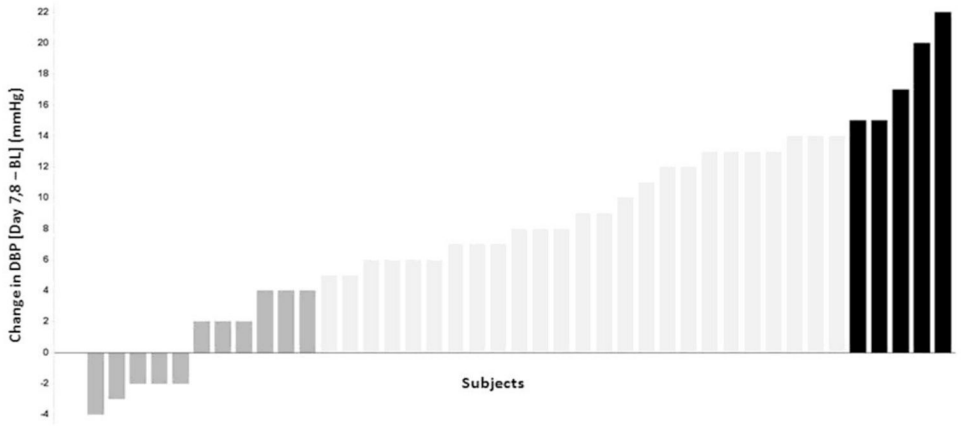

Figure 2. Distribution of changes in DBP (Day 7,8 – BL)

Each bar represents change in mean of diastolic blood pressure for each patient between Day 7,8 and baseline pre-treatment measurement. Dark gray bars are subjects with < 5 mmHg increase (within limits of quantitation of the device), light gray bars are subjects with ≥ 5 mmHg and < 15 mmHg increase, black bars are subjects with ≥ mmHg increase, mmHg = millimeters mercury

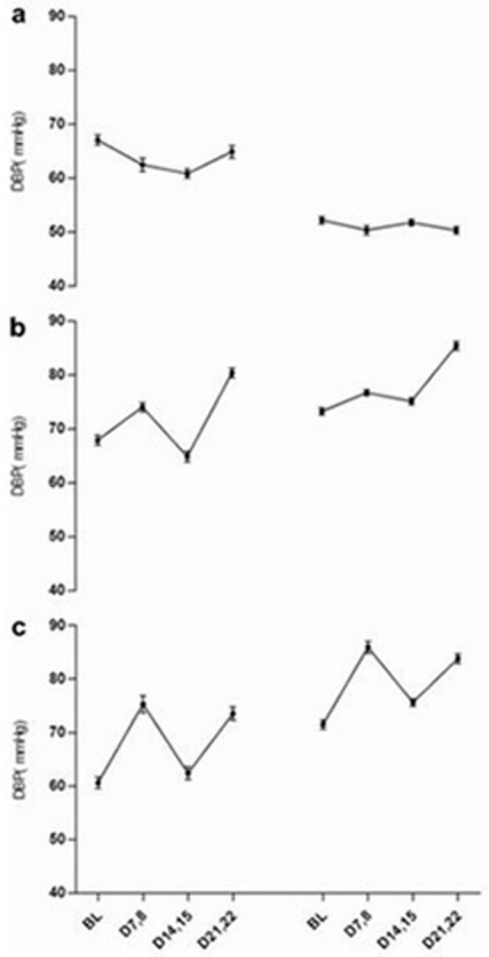

Figure 3. Example blood pressure response patterns to sorafenib

Each of the six plots depicts a patient's mean 12-hour DBP for the 4 ABP monitoring sessions. The error bars represent the standard error of the mean DBP. For each of the 3 examples, the patient on the left was assigned to Arm A and the patient on the right to Arm B. a) BP-resistant patients, b) dose-sensitive patients, c) dose-insensitive patients. BL = baseline, D7–8 = Days 7 or 8, D14–15 = Days 14 or 15, D21–22 = Days 21 or 22; DBP = diastolic blood pressure, mmHg = millimeters mercury

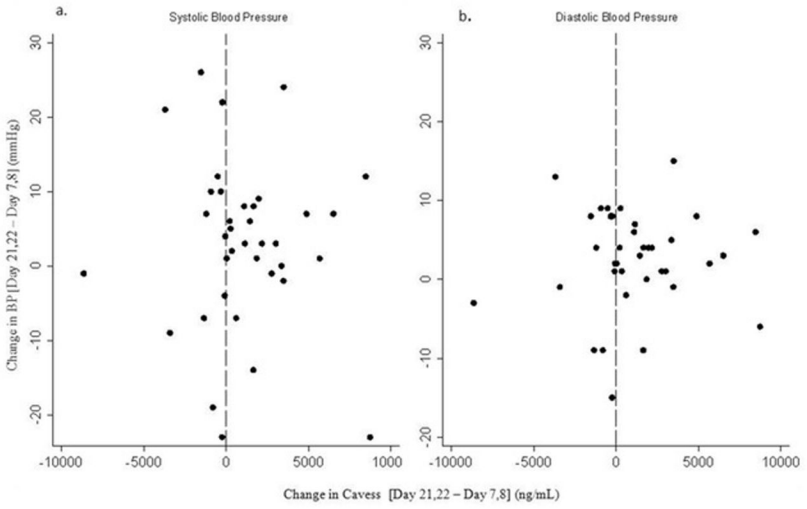

Figure 4. Change in sorafenib plasma concentrations and the change in BP (Day 21, 22–Day 7, 8)

Change in mean steady state plasma concentrations (C_{avess}) between Days 21, 22 and Day 7, 8 for all evaluable patients and the change in mean BP between the two sessions. ng/ml = nanograms/milliliter; BP = diastolic blood pressure, mmHg = millimeters mercury. a) SBP (systolic blood pressure) and b) DBP (diastolic blood pressure)

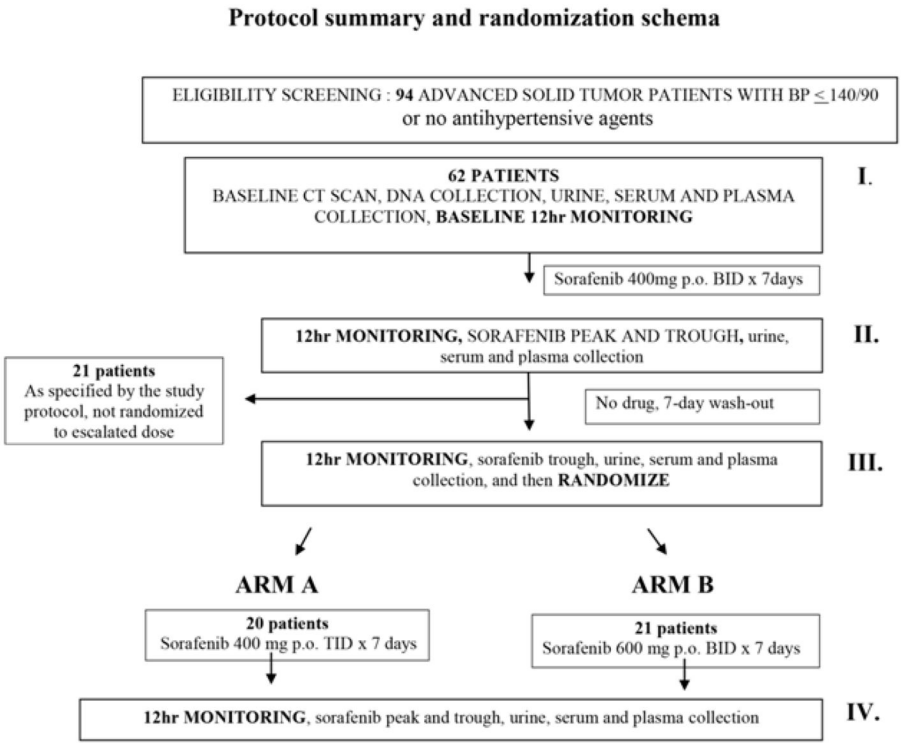

Figure 5. CONSORT DIAGRAM

Eligibility screening through Day 22 of sorafenib treatment

Table 1

Characteristics of evaluable randomized patients

Characteristics	Arm A	Arm B	Total N (%)
Sex			
Women	12	10	22 (54)
Men	8	11	19 (46)
Self-reported race/ethnicity			
White non-Hispanic	16	16	32 (78)
Black non-Hispanic	3	4	7 (17)
White-Hispanic	1	1	2 (5)
Age (y)*	49 (19–66)	53 (20–73)	51 (19–73)
Body mass index (kg/m^2)*	26 (17–37)	29 (18–38)	27 (17–38)
Tumor Type			
Thyroid carcinoma	5	3	8 (19)
Head and Neck	4	2	6 (15)
Sarcoma	2	3	5 (12)
Breast	2	2	4 (10)
NSCLC	1	3	4 (10)
Neuroendocrine	1	2	3 (7)
Other*	5	6	11(27)

*y, years; kg/m2, kilograms per square meter,

*Includes 1 patient with gastric, ovarian, SCLC, Wilms and unknown primary carcinoma, 2 patients each with pancreatic, cholangiocarcinoma and esophagus cancer

Table 2

Toxicities of escalated dose sorafenib

Adverse Events (AE)	Arm A	Arm B
Total # of AE*		
≥ grade 2 hypophosphatemia	12	11
≥ grade 2 hand foot syndrome	4	6
≥ grade 2 lipase	4	4
Timing of AE		
Cycle 1	5	5
Cycle 2	7	5
Patients		
# of pt. continued on escalated dose post cycle 2	8	11

*Some patients had more than one AE

Table 3

Blood pressure effects of sorafenib during first week of standard dose treatment

	Arm A (n=20)			Arm B (n=21)		
	BL	**D7,8**	**ΔBP**	**BL**	**D7,8**	**ΔBP**
SBP						
Mean	120.7	130.5	9.9	127.3	139	11.6
SD	10.2	16.2	12.3	11.4	9.6	7.6
Median	118	128	10	125	139	14
Range	101.0–137.0	108.0–169.0	8.0–43.0	111–151.0	121.0–158.0	5.0–20.0
95% CI			4.1–15.7			8.2–15.1
P			**0.0019**			**<0.0001**
DBP						
Mean	72.9	80.7	7.9	73.4	81.7	8.2
SD	6.8	10.6	7.2	7.6	9	5.2
Median	74.5	78.5	6.5	73	83	8
Range	61.0–88.0	63.0–99.0	−4.0–22.0	52.0–85.0	49.0–92.0	−3.0–17.0
95% CI			4.5–11.2			5.9–10.6
P			**0.0001**			**<0.0001**

Abbreviations: BL, baseline; D7,8, Day 7 and 8; BP, blood pressure; SBP systolic blood pressure; DBP, diastolic blood pressure, ΔBP=D7,8-BL